USDA Research, Development, Translation, and Validation Activities

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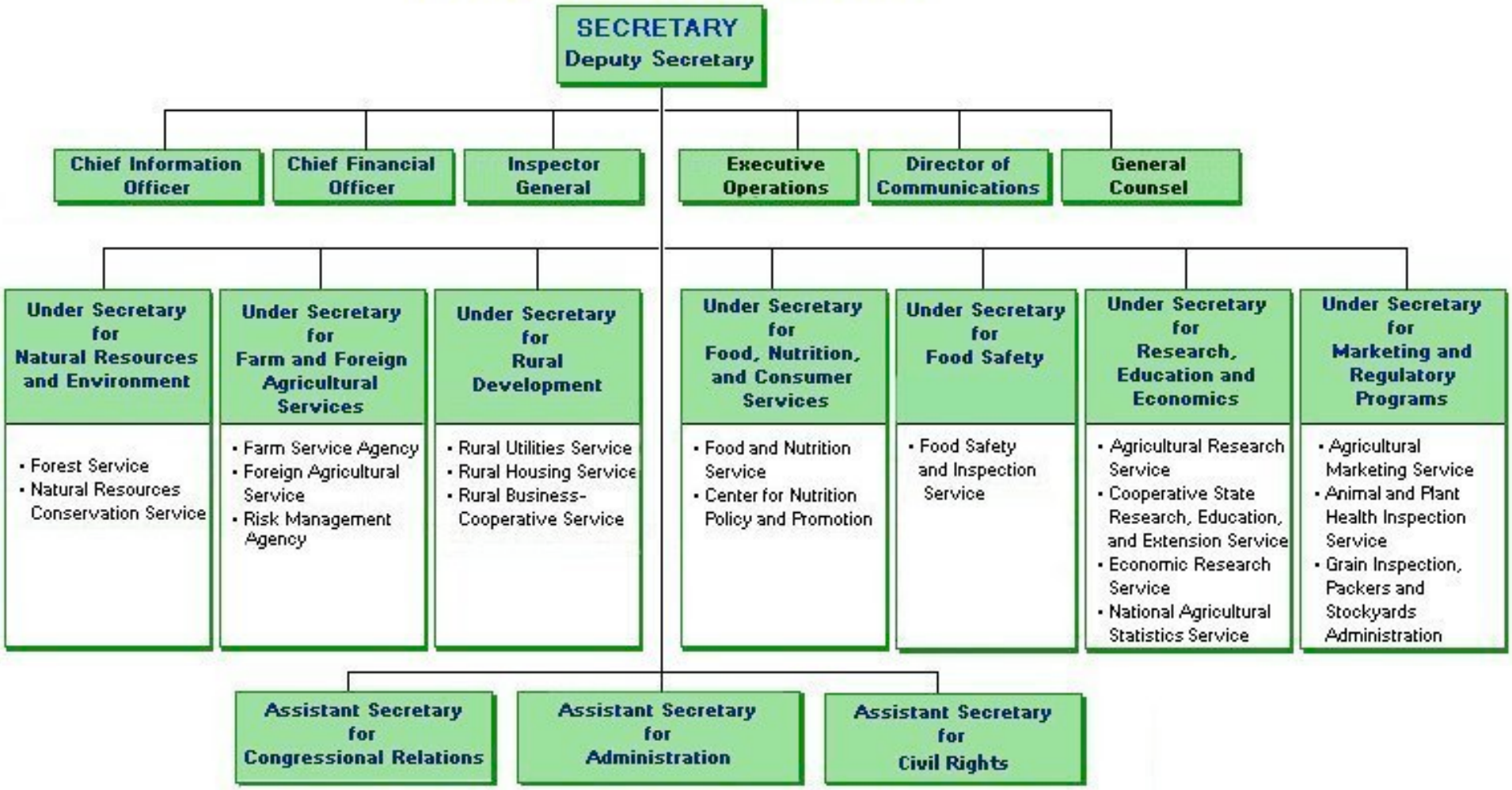
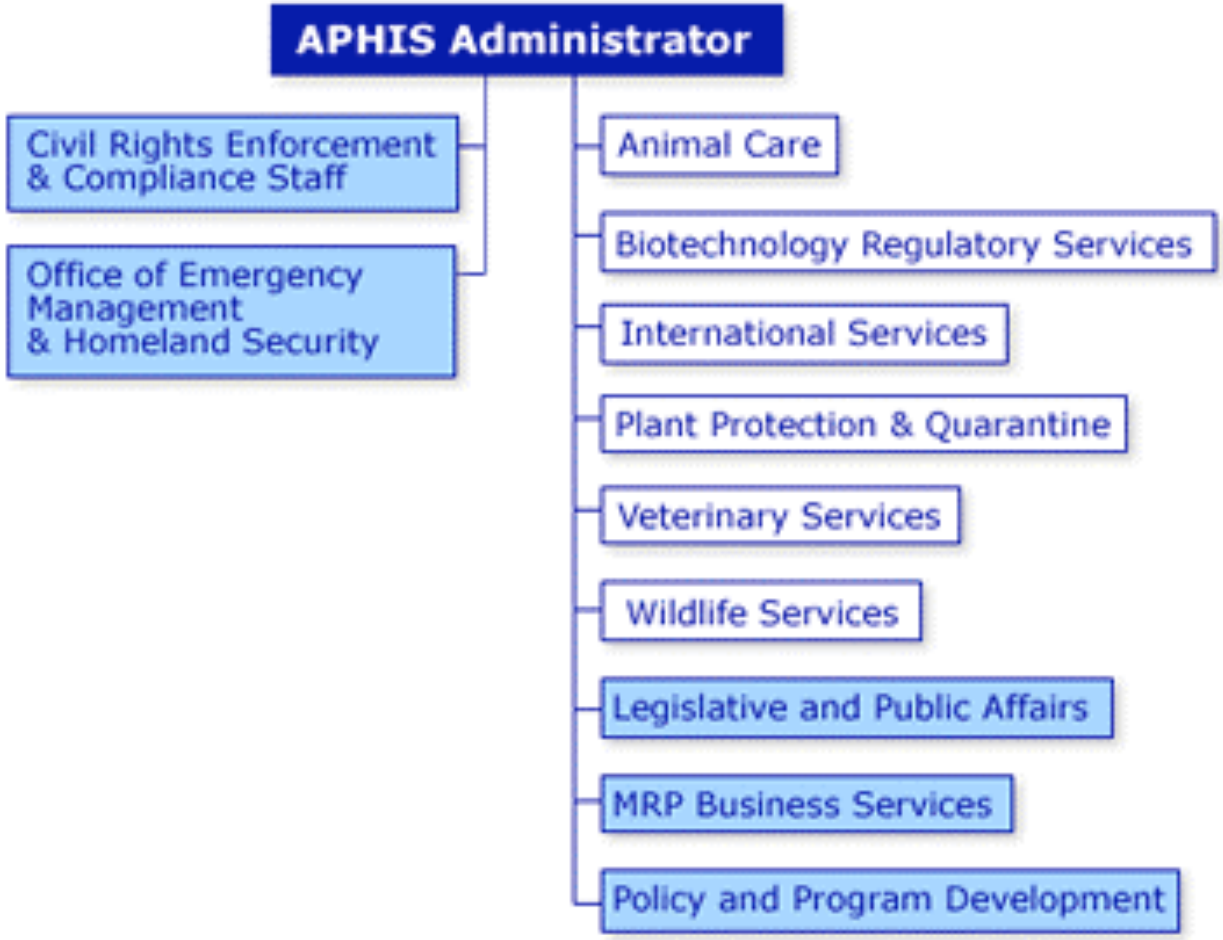
Headquarters Organization

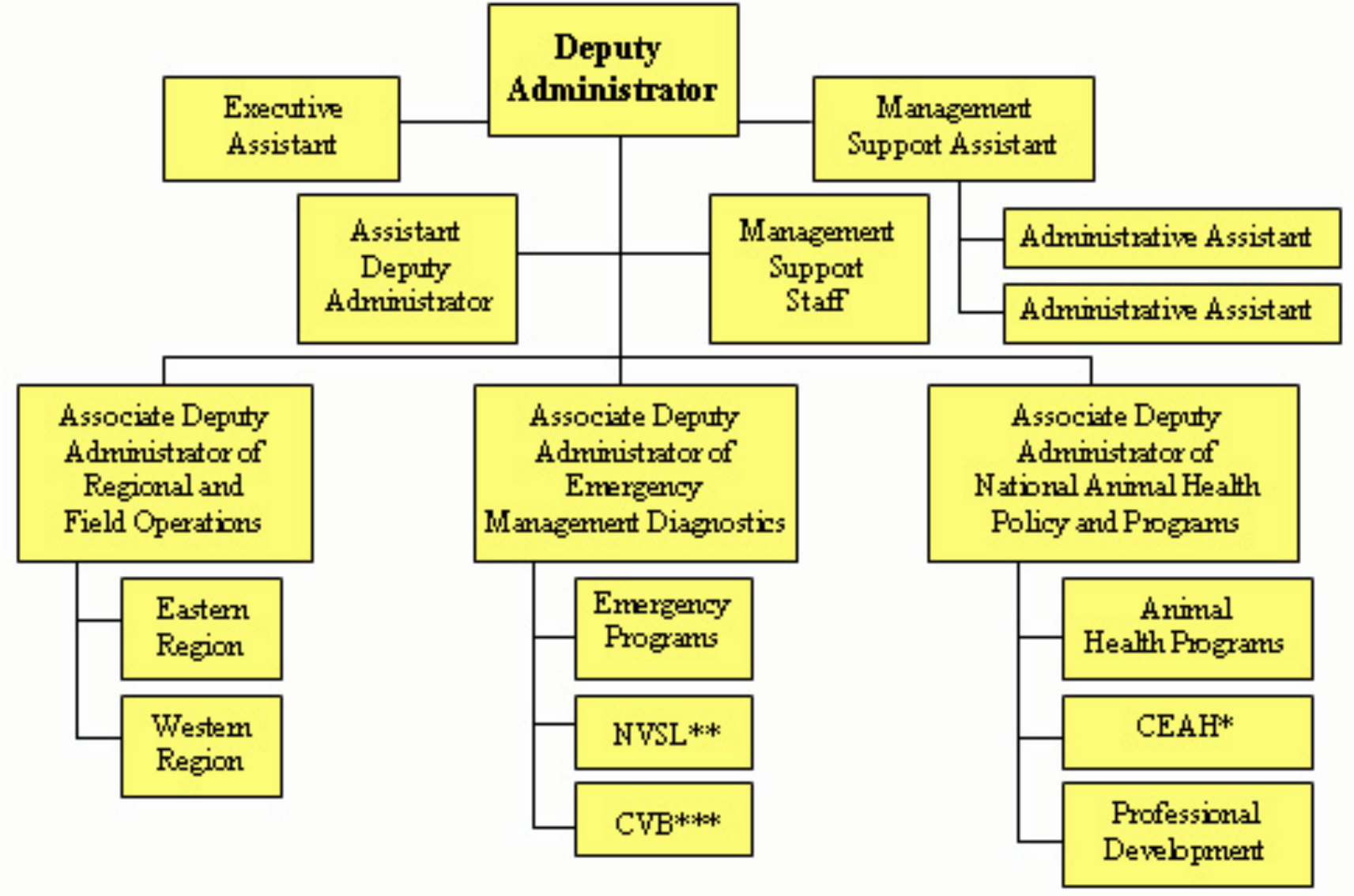


Updated April 2003

USDA-Animal and Plant Health Inspection Service

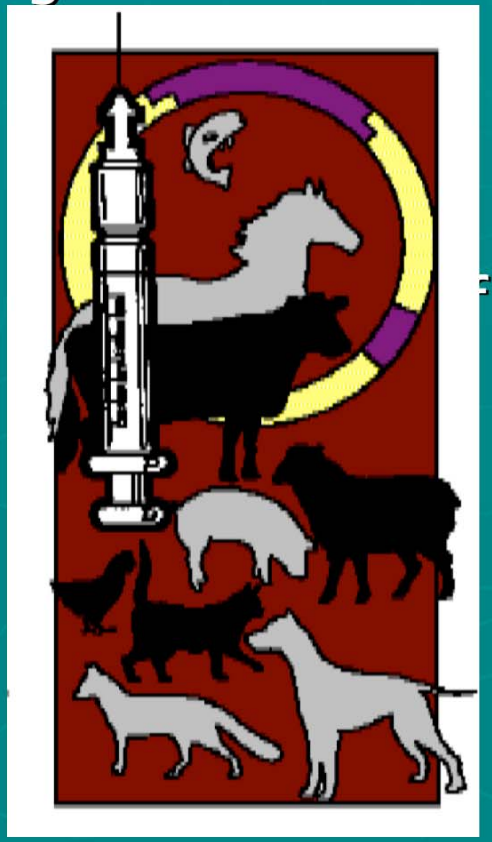


USDA-APHIS-Veterinary Services



Center For Veterinary Biologics

- Authority derives from the "Virus-Serum-Toxin Act"
- Responsible for regulating veterinary biologics:
- Vaccines
- Bacterins
- Antisera
- Diagnostic kits, and other products biological origin
- Ensure they are pure, safe, potent, and effective.



Veterinary Biologics Testing

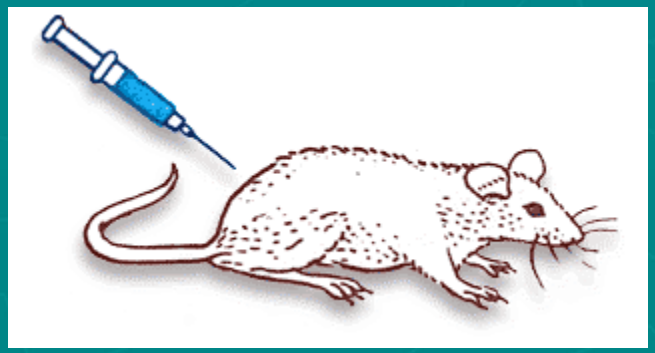
- Purity: Ensure product is not contaminated
- Safety: Ensure product is not dangerous or harmful
- Potency/Efficacy: Ensure product is not worthless

Potency Testing

- The purpose of potency testing is to provide assurance the active component(s) required for the efficacy of the vaccine is/are present at a concentration and in a state that has been shown to be efficacious in the host animal.

Potency Testing

- 1960-1970's
- All vaccines required vaccination and challenge of target species, or surrogate laboratory animals, for serial release



Potency Testing

- 1960-1970's
- Potency testing of modified live virus vaccines was replaced by quantification of the live organisms (titration)
  - Major step toward reducing animal use and first example of in vitro potency testing
  - "Master Seed" principle introduced

Impact on Animal Usage

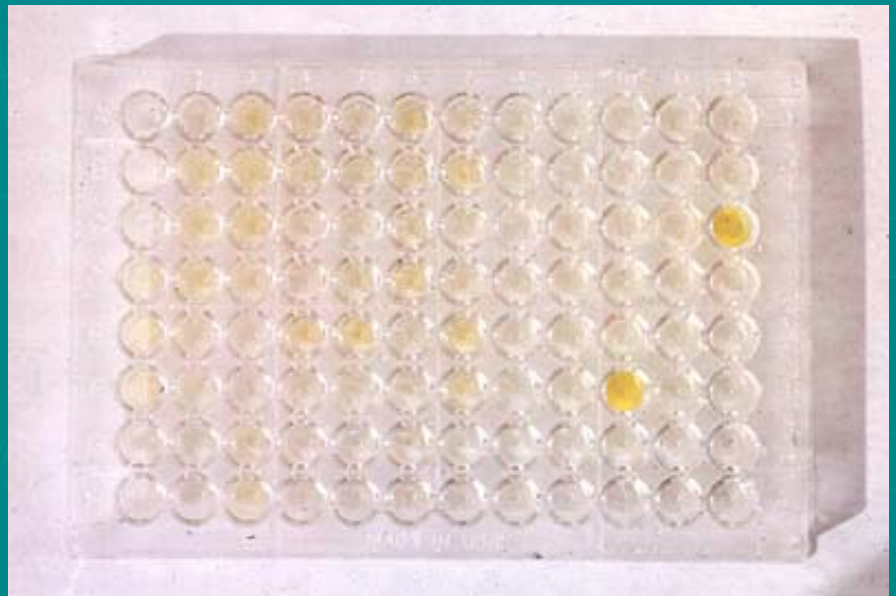
Type of Vaccine	ML Products	Total Products	
Viruses	417	626	67%
Bacterins/Extracts	0	179	0%
Bacterin-Toxoids	0	70	0%
Toxoids	0	15	0%
FFM	78	171	46%
TOTAL	639	1314	47%

Potency Testing

- 1980's - Present
  - Regulation changed from "Virus titration in lieu of animal test for immunogenicity" to "In vitro tests ..."
  - Expanded coverage to both live viral and bacterial vaccines

Potency Testing

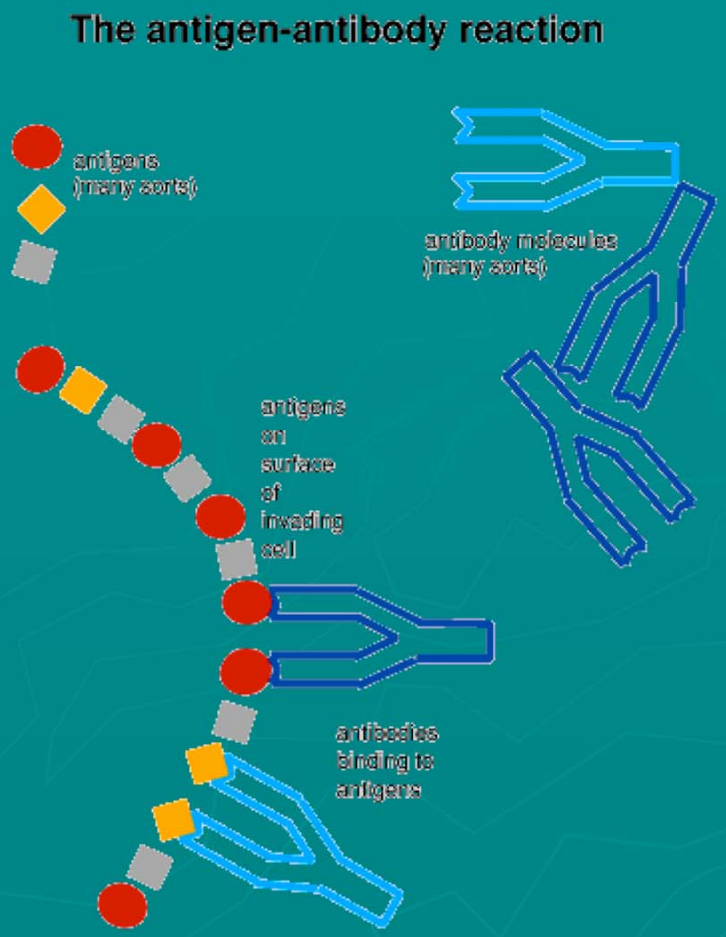
- 1980's - Present
- In 1997, the regulation was revised to include information on potency testing by relative antigen content as outlined in 9 CFR 113.8 and VS Memorandum 800.90.



Could *theoretically* be used for many products

Replacement Methods

- In Vitro Assays:
  - Usually measure a single antigen/epitope known to contribute to protection in host.
  - Release values can be absolute or relative.
  - Best in vitro assays are sensitive, specific, reproducible, inexpensive, and rapid (easily automated).



Replacement Methods

- In Vitro Assays:
- Drawbacks:
  - Measure only one, or a limited set of, antigens and fail to evaluate other protective antigens or other vaccine components.
  - RP assessments often cannot determined if the active agent is present in high or minimally acceptable levels.
  - Adjuvants may interfere with the assay and must be removed.
  - Unless conformational Mabs are utilized, in vitro assays typically do not differentiate antigen that is biologically active from denatured antigen.

USDA Research, Development, Translation, and Validation Activities

NICEATM-ICCVAM

Five-Year Plan

(2008-2012)

Clostridium haemolyticum

- Bacterial toxin
- Western US
- Cattle and sheep
- Hemoglobinuria, jaundice, death

Clostridium haemolyticum

- 9 CFR 113.107
- Guinea Pigs
- 8-10 vaccinates, 5 controls
- Challenge test (4/5 controls must die)

Clostridium haemolyticum

- Science Fellow project (2003-2007)
- Did develop monoclonal antibodies
- No further funding available; project is on hold

Leptospira serovars

- pomona, canicola, grippotyphosa, and icterohaemorrhagiae
- Dogs, livestock
- Jaundice, fever, kidney failure

Leptospira serovars

- 9 CFR 113.101, 102, 103 and 104
- Hamsters
- 10 vaccinates, 10 controls
- Challenge test (8/10 controls must die)

Leptospira serovars

- Dog data completed December 2006
- CVB Notice 07-02 released March 2007; CVB Notice 07-12 released July 2007
- Pig data completed April 2008
- Under review within USDA
- Establishes a Standard Reference Bacterin, distributed by CVB, that may be used for an in vitro potency assay

Rabies

- Virus
- All warm-blooded species
- Affects the central nervous system, and is almost always fatal

Rabies

- 9 CFR 113.209
- Mice
- 25 vaccinates, 10 controls
- Challenge test with an established humane endpoint (paresis, paralysis, convulsions)

Refinement Methods

- Rabies Vaccine challenge test in mice
- Score 1: ruffled fur, hunched back
- Score 2: slow movements, circling plus >15% weight loss
- Score 3: trembling, shaky, convulsions
- Score 4: lameness, paralysis, permanent recumbency

Rabies

- Science Fellow proposal to develop an in vitro assay submitted in 2008
- Approved, but not funded
- Currently participating in a collaborative study organized by EDQM to correlate mouse serology to the challenge test
- Further refinement to the current in vivo test

Alternative Methods

- An on-going goal for the Center for Veterinary Biologics has been the reduction of animals used for mandatory 9 CFR testing.
- CVB encourages manufacturers to submit alternative methods for animal potency assays.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Discussion Questions (1)

- With regard to the current portfolio of agency activities and their applicability to the development and validation of alternative test methods that will further reduce, refine, and replace animal use for regulatory safety testing:
- Are there any gaps in the portfolio?
- Are there areas that should be strengthened?

- How might NICEATM and ICCVAM strengthen their leadership role in identifying and promoting R&D activities among the 15 Federal agencies represented on ICCVAM that would produce alternative methods applicable to regulatory testing needs?

Discussion Questions (2)

- Based on the agency activities described, are there any activities that might benefit from interaction with ICCVAM and any of the ICCVAM test method working groups at this time?

- Have these additional presentations addressed previous SACATM questions regarding (1) development and validation of alternative methods, (2) the prioritization of research on activities relevant to the Five-Year Plan (3) stakeholder involvement and collaboration, (4) coordination of high throughput screening projects, and (5) toxicants utilized in research?